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Title: Characterization of point mutations and deletion mutations in a series of null alleles at the triosephosphate isomerase locus in humans and mice.

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Text: Null alleles have been identified at the triosephosphate isomerase (TPI) locus during the screening for activity of 10 erythrocyte enzymes in ~2000 newborn children (Pediatr. Res. 16:960-963, 1982; Hum. Genet. 77:241-245, 1987) and in mouse germinal experiments (W. Pretsch, pers. comm.). In the human population, the frequency of TPI null alleles was approximately 10 fold greater in the African American population (0.02) than in the Caucasian population (0.0024). In the case of point mutations, genomic PCR products were sequenced. For the analysis of heterozygous gene deletions, PCR products were quantitated by Perfusion HPLC. We report the characterization of heterozygous TPI deletions in 3 mouse mutants. Among the human population, we describe the molecular characterization of the null alleles from 7 African American and 3 Caucasian individuals. Whereas 3 different amino acid substitutions were identified in the 3 Caucasians, a common variant allele consisting of two nucleotide changes immediately 5' of the transcription initiation site was found in the 7 unrelated African Americans. Two of the 3 amino acid substitutions had not been described previously and occurred at residues not directly involved in the active site but highly conserved through evolutionary time. This suggests important roles for these residues in maintenance of subunit structure and conformation. The combined results from human and mouse studies provide insight into the mechanism of mutations and serve as models for structure-function studies. Work performed under auspices of the US DOE by Lawrence Livermore National Laboratory; contract W-7405-ENG-48.